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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	**PAPER NUMBER**
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,901	NEFF ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *0904* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed November 3, 2004 has been entered.

Claims 1, 12 and 22 are currently amended.

Claims 33-41 are newly added.

Claims 1-41 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, filed November 3, 2004 is attached to the instant Office action.

Claim Rejections - 35 USC § 112

Claims 1, 12 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Claims 1, 12 and 22 recite the limitation "which converts an active brassinosteroid to an inactive brassinosteroid". This limitation does not find support in the specification as originally filed and thus constitutes new matter. Applicants' indication at page 7 of the reply that support for this amendment can be found at

page 5 of the specification is acknowledged. However, the disclosure at page 5 of the specification does not support this amendment in that the disclosure indicates only that CYP72B1 (i.e. BAS1) "is a C-26 hydroxylase of brassinolide, targeting it for inactivation". Such a disclosure does not support a limitation directed to any type of unspecified conversion by BAS1 of any type of unspecified active brassinosteroid to any type of unspecified inactive brassinosteroid.

Claims 1-4, 7-13, 15, 17-23, 25 and 27-32 remain rejected, and newly added claims 33-41 are rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the office action mailed June 3, 2004.

Applicants' arguments filed November 3, 2004 have been fully considered but they are not persuasive.

Applicants maintain that the rejection is avoided by the amendments to the claims. Applicants have amended claims 1 and 12 (and those dependent thereon) to recite that the BAS1 polypeptide is a cytochrome P450 which converts an active brassinosteroid to an inactive brassinosteroid. Applicants maintain that the amendment of the claims to include the substrate for the BAS1 polypeptide provides a key structural feature unique to the genus. (reply page 8)

The Examiner disagrees that amendment of the claims to include the substrate for the BAS1 polypeptide provides a key structural feature unique to the genus. The outstanding

rejection was based on the failure to describe structural genes encoding other BAS1 polypeptides that are obtained from sources other than *Arabidopsis* or *Catharanthus roseus*, and a substrate is not a structural feature of a structural gene or its encoded polypeptide. Furthermore, the amended claims make no reference to a "substrate".

Applicants also point out that at the time of the filing of the present application a large number of representative species falling within the scope of the claimed genus were known, and that in fact, more than 200 P450 sequences were known (see Werck-Reichhart D. and Feyereisen P., Cytochromes P450: a success story. Genome Biol. 2000;1(6):3003.1-3003.9, Applicants' IDS filed November 3, 2004 Ref. No. 5). Applicants point out that from years of studies of P450 enzymes, there is a large body of work including several crystal structures of cytochrome P450s (see Werck Reference pages 3003.2-3003.3), and that the entire catalytic cycle of the cytochrome P450s, determined from a series of crystal structures captured through the cycle, was published contemporaneous to the priority date of the application, and even then only three of the seven intermediate structures in the catalytic pathway were new (see Schlichting I. et al., The catalytic pathway of cytochrome p450cam at atomic resolution. Science. 2000 Mar 3;287(5458):1615-22, Applicants' IDS filed November 3, 2004 Ref. No. 3). Applicants point out that, as detailed in the review, the cytochrome P450s all have the same structural fold and all share the same enzymatic mechanism. Applicants maintain that a large number of species falling within the scope of the claimed genus of sequences comprising at least one structural gene encoding a BAS 1 polypeptide (where the BAS 1 polypeptide is a cytochrome P450) were thus known to those of skill in the art at the time the application was filed. (reply pages 8-9)

The Examiner disagrees that a large number of representative species falling within the scope of the claimed genus were known at the time of filing. The rejected claims do not encompass the use of sequences encoding any and all cytochrome P450 polypeptides. The rejected claims are limited to a specific subgenus of sequences encoding cytochrome P450 polypeptides, ie sequences encoding cytochrome P450 polypeptides which function to convert an active brassinosteroid to an inactive brassinosteroid. While the references cited by Applicants describe the genus of sequences encoding cytochrome P450 polypeptides, the references cited by Applicants do not specifically describe the subgenus of sequences encoding cytochrome P450 polypeptides which function to convert an active brassinosteroid to an inactive brassinosteroid. A description of the genus of sequences encoding cytochrome P450 polypeptides does not adequately describe the subgenus of sequences encoding cytochrome P450 polypeptides which function to convert an active brassinosteroid to an inactive brassinosteroid because different types of cytochrome P450 polypeptides are known to utilize different substrates and affect different biochemical pathways. See, for example, the cited reference of Werck-Reichhart D. and Feyereisen P. (abstract):

> Canonical P450s use electrons from NAD(P)H to catalyze activation of molecular oxygen, leading to regiospecific and stereospecific oxidative attack of a plethora of substrates. The reactions carried out by P450s, though often hydroxylation, can be extremely diverse and sometimes surprising. They contribute to vital processes such as carbon source assimilation, biosynthesis of hormones and of structural components of living organisms, and also carcinogenesis and degradation of xenobiotics.

See also, for example, the cited reference of Schlichting I. et al. (page 1615 column 1 first paragraph):

> Cytochrome P450 enzymes are ubiquitous heme-containing monooxygenases named for the absorption band at 450 nm of their carbon monoxide (CO) form (1). They are involved in a number of vital processes including carcinogenesis and drug metabolism as

well as the biosynthesis of steroids or lipids and the degradation of xenobiotics (2), making them potentially useful in, e.g., bioremediation or synthesis.

Applicants further point out that because of the vast information known about cytochrome P450s including sequence alignments, mutagenic data and crystal structures relating the important residues in the sequence to the known catalytic function, the structural features unique to the genus (cytochrome P450) were known. Applicants maintain that they have further identified a functional feature of the cytochrome P450 genus by identifying the substrate of the disclosed cytochrome P450 as active brassinosteroids and the function of the disclosed cytochrome P450 as catabolism of the active brassinosteroids, i.e., inactivation of the brassinosteroids. Applicants point out that the claims have been amended to require that the cytochrome P450 of the invention uses as its substrate an active brassinosteroid, and maintain that one of skill in the art can readily identify the range of cytochrome P450 sequences that will likely bind to active brassinosteroid substrate. Applicants point by way of example to a recently published paper using amino acid sequences, crystal structures, and modeling programs available as of the priority date of this application which demonstrates that four highly divergent plant cytochrome P450s share similar structurally based strategies for substrate binding. (see Rupasinghe S. et al. Common active site architecture and binding strategy of four phenylpropanoid P450s from *Arabidopsis thaliana* as revealed by molecular modeling. Protein Eng. 2003 Oct;16(10):721-31, Applicants' IDS filed November 3, 2004 Ref. No. 2). Applicants point out that they have identified a sequence, i.e., BAS1, and a substrate, i.e., active brassinosteroid, and maintain that these data, together with crystal structure modeling programs, will allow one to identify related BAS1 sequences useful in the practice of the invention.

Applicants thus maintain that one of skill in the art would understand that Applicants had possession of the invention at the time of filing the application because of (a) the large number of known cytochrome P450 sequences; (b) the readily determinable relationship between the structure and the function binding of the substrate - an active brassinosteroid; (c) the ease of producing a plant from a transformed plant cell and (d) the ease of selecting plants exhibiting a dwarf adult stature. (reply pages 9-10)

The Examiner maintains that the amended claims make no reference to a "substrate", and that the specification does not disclose the function of BAS1 as converting an active brassinosteroid to an inactive brassinosteroid. The Examiner also maintains that the disclosure of a specific function for BAS1 coupled with the disclosure of BAS1 as a cytochrome P450, absent a description of the specific structural features of BAS1 that are correlated with this specific function, does not satisfy the written description requirement for all cytochrome P450s having the same specific function as BAS1, since different types of cytochrome P450s exhibit different specific functions. The Examiner additionally maintains that whether a sequence is described is not dependent on whether the specification provides an enabling disclosure. See *University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997), which discusses the description of a claimed human cDNA sequence based on the disclosure of a rat cDNA sequence and a method for obtaining the human cDNA sequence:

> The patent describes a method of obtaining this cDNA by means of a constructive example, Example 6. This example, however, provides only a general method for obtaining the human cDNA (it incorporates by reference the method used to obtain the rat cDNA) along with the amino acid sequences of human insulin A and B chains. Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin, which is necessary to provide a written description of the subject matter of claim 5. The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its

> identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. (*Lilly*, 43 USPQ2d at 1405)

The Examiner further maintains that a showing of possession alone cannot substitute for a description of the claimed sequences. See *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1617:

> Application of the written description requirement, however, is not subsumed by the "possession" inquiry. A showing of "possession" is ancillary to the *statutory* mandate that "[t]he specification shall contain a written description of the invention," and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention. After all, as indicated above, one can show possession of an invention by means of an affidavit or declaration during prosecution, as one does in an interference or when one files an affidavit under 37 C.F.R. § 1.131 to antedate a reference. However, such a showing of possession alone does not cure the lack of a written description in the specification, as required by statute.

Claims 1-4, 7-13, 15, 17-23, 25 and 27-32 remain rejected, and newly added claims 33-41 are rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a genetically modified plant characterized as having dwarf adult stature, including a genetically modified plant that exhibits green foliage that is darker than a wild-type plant, by transforming a plant with an exogenous nucleic acid sequence encoding a BAS 1 polypeptide having the amino acid sequence of SEQ ID NO:2, does not reasonably provide enablement for methods of transforming plants with other exogenous nucleic acid sequences of unspecified sequence encoding other BAS 1 polypeptides obtained from unspecified sources, or for methods of transforming plants with other exogenous nucleic acid sequences at least 80% identical to SEQ ID NO:1 or encoding polypeptides at least 80%

identical to SEQ ID NO:2 or hybridizing to SEQ ID NO:1 under defined conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record set forth in the office action mailed June 3, 2004.

Applicants' arguments filed November 3, 2004 have been fully considered but they are not persuasive.

Applicants maintain that the specification provides more that adequate support to enable one of skill in the art to make and use the claimed invention commensurate in scope with the claimed invention, and that application of the Wands factors to the claimed invention clearly supports this assertion (reply page 10)

Applicants maintain that the quantity of experimentation necessary to practice the claimed invention is not undue. Applicants point out that the techniques required to practice the claimed invention are routine, and that the quantity of experimentation necessary to practice the claimed invention is therefore not undue. Applicants also maintain that the identification of cytochrome P450s which use active brassinosteroids as substrate is a routine matter, and Applicants reiterate that there is a vast wealth of knowledge available regarding cytochrome P450s. Applicants maintain that that this vast knowledge reduces the experimentation needed by allowing those of skill in the art to reject sequences that will clearly not function based upon knowledge of the key residues involved in function of the cytochrome P450s, for example, enzymatic activity and substrate specificity, and upon knowledge of regions of high sequence variability that do not affect function. (reply pages 10-11)

The Examiner disagrees that the quantity of experimentation necessary to practice the claimed invention is not undue. The quantity of experimentation necessary to practice the claimed invention is not necessarily undue just because the techniques required to practice the claimed invention are routine, given that the outstanding rejection was not based on the unpredictability of the techniques required to practice the claimed invention, but on the unpredictability of selecting a sequence encoding a polypeptide having the functional characteristics of BAS1 on the basis of its identity as a cytochrome P450 protein (page 6 of the office action mailed June 3, 2004). The quantity of experimentation necessary to practice the claimed invention is also not necessarily undue just because there is a vast wealth of knowledge available regarding cytochrome P450s, since different types of cytochrome P450 proteins are not functionally interchangeable. The issue here is not whether the identification of cytochrome P450s which use active brassinosteroids as substrate is a routine matter, but whether the identification of cytochrome P450s which act in the same manner on the same substrate(s) as BAS1 is a routine matter. The Examiner maintains that neither the disclosure nor the pre or post filing date art establish that cytochrome P450s which act in the same manner on the same substrate(s) as BAS1 may be routinely identified, as only a single species of BAS1 polypeptide has been characterized.

Applicants also maintain that an adequate amount of guidance is provided with respect to how to identify additional sequences. Applicants point out that where the nature of the experimentation required to practice the claimed invention is routine, the techniques to be used need not be disclosed, and yet Applicants have disclosed such techniques in actual working

examples. Applicants further point to the specification, at page 59, which discusses methods of identifying additional BAS l-encoding genes, by hybridization techniques and degenerate PCR techniques, for example. (reply page 11)

The Examiner disagrees that the amount of guidance provided is sufficient. The disclosure of a single gene sequence from a single species of organism encoding a polypeptide belonging to an art recognized class of proteins does not provide sufficient guidance to enable the full scope of the rejected claims because, as discussed above, cytochrome P450 proteins are known to be functionally diverse. The Examiner also disagrees that the nature of the experimentation required to practice the claimed invention is routine. While the disclosed plant transformation and recombinant DNA techniques are within the technical abilities of one skilled in the art, it has not been established that the disclosed techniques may be readily employed to obtain other sequences encoding other polypeptides having the functional characteristics of BAS1, as only a single cytochrome P450 polypeptide having the functional characteristics of BAS1, i.e. BAS1, is disclosed or known.

Applicants additionally maintain that the working examples provided support the enablement of the invention as claimed. Applicants point out that they have taught actual working examples of the BAS1-encoding gene and plants transformed with one such gene. Applicants point in particular to Examples 1-3 which teach the isolation of a BAS1 encoding gene, as well as other examples that provide an abundant disclosure characterizing the functional and structural characteristics of the expression of BAS1, including effect on plant size, brassinolide dose reply response, and biochemical analysis of the enzymatic activity. (reply

pages 11-12)

The Examiner acknowledges Applicants' disclosure of working examples but maintains that the examples provided, which utilize a single BAS1 coding sequence, are not commensurate in scope with the rejected claims, which are directed to the use of a multitude of unknown and undisclosed gene sequences obtained from any source that encode a cytochrome P450 which converts in any unspecified manner any unspecified active brassinosteroid to any unspecified inactive brassinosteroid.

Applicants maintain that the nature of the invention weighs in favor of enablement because making and using the invention requires only routine molecular biology techniques and is a matter of routine testing of sequences related to those disclosed. Furthermore, in this instance, Applicants point out that the basl gene is part of a large family of enzymes that share the same mechanism and differ primarily in substrate preference. (reply page 12)

The examiner disagrees that the nature of the invention weighs in favor of enablement, because of the unpredictability of selecting a sequence encoding a polypeptide having the functional characteristics of BAS1 on the basis of its identity as a cytochrome P450 protein, which unpredictability is not mitigated by the use of routine molecular biology techniques, or by the fact that the basl gene is part of a large family of enzymes that share the same mechanism and differ primarily in substrate preference.

Applicants maintain that the state of the prior art weighs in favor of enablement because the state of the art is high. Applicants point out that as of the priority date of March 16, 1999,

molecular biology techniques were well worked out and included a high degree of automation due to, for example, genome sequencing. Additionally, Applicants point out that the cytochrome P450 field is very well developed with a large number of identified sequences and abundant structural, biochemical and mutagenic data available to give guidance to one of skill in the art to identify additional BAS1 polypeptides that have a high likelihood of functioning. (reply page 12)

The Examiner disagrees that the state of the prior art weighs in favor of enablement. The rejection was not predicated on the state of the art with respect to molecular biology techniques, but on the failure to provide sufficient guidance with respect to where and how to obtain exogenous nucleic acid sequences encoding BAS1 polypeptides obtained from sources other than *Arabidopsis* or *Catharanthus roseus* plants, and on the unpredictability of selecting a sequence encoding a polypeptide having the functional characteristics of BAS1 on the basis of its identity as a cytochrome P450 protein (page 6 of the office action mailed June 3, 2004). Additionally, as discussed above, different types of cytochrome P450 polypeptides are known to utilize different substrates and affect different biochemical pathways (Werck-Reichhart D. and Feyereisen P. and Schlichting I. et al. cited above). Accordingly, the fact that the cytochrome P450 field is very well developed with a large number of identified sequences and abundant structural, biochemical and mutagenic data available alone does not give guidance sufficient guidance to one of skill in the art to identify additional BAS1 polypeptides that have a high likelihood of functioning in the same manner as BAS1 functions, as only a single cytochrome P450 polypeptide having the functional characteristics of BAS1, i.e. BAS1, is disclosed or known.

Applicants maintain that the relative skill of those in the art weighs in favor of enablement because the skill in the art is high. Applicants point out that plant transformation is typically done by graduate level research scientists or higher, and that such research scientists are well versed in the molecular biology and screening techniques required by the claimed invention. (reply page 12)

The Examiner maintains that the rejection was not predicated on the relative skill of those in the art, which is acknowledged to be high, but on the failure to provide sufficient guidance with respect to where and how to obtain exogenous nucleic acid sequences encoding BAS1 polypeptides obtained from sources other than *Arabidopsis* or *Catharanthus roseus* plants, and on the unpredictability of selecting a sequence encoding a polypeptide having the functional characteristics of BAS1 on the basis of its identity as a cytochrome P450 protein (page 6 of the office action mailed June 3, 2004).

Applicants maintain that the predictability of the art weighs in favor of enablement in view of the vast body of knowledge regarding cytochrome P450 enzymes, and the ease with which transgenic plants can be generated, the predictability of the art pertaining to the invention is high. Applicants point out that a large number of P450 enzymes have been identified, and that sequence alignment studies, along with computer models of crystal structures of the enzymes, have allowed the identification of regions of the P450s that may vary with no change in function. Furthermore, Applicants point out that the production of transgenic plants is quite predictable, and that the high predictability of the plant transformation techniques permits even students to successfully perform experiments in a timely and reproducible manner. Applicants submit that

the vast array of available information on P450 enzymes coupled with the high predictability of making transgenic plants with Bas-1 related sequences can readily and predictably be used to identify Bas-1 related sequences. (reply pages 12-13)

The Examiner disagrees that the predictability of the art weighs in favor of enablement. The rejection was not predicated on the unpredictability of plant transformation techniques, but on the failure to provide sufficient guidance with respect to where and how to obtain exogenous nucleic acid sequences encoding BAS1 polypeptides obtained from sources other than *Arabidopsis* or *Catharanthus roseus* plants, and on the unpredictability of selecting a sequence encoding a polypeptide having the functional characteristics of BAS1 on the basis of its identity as a cytochrome P450 protein (page 6 of the office action mailed June 3, 2004). Additionally, as discussed above, different types of cytochrome P450 polypeptides are known to utilize different substrates and affect different biochemical pathways (Werck-Reichhart D. and Feyereisen P. and Schlichting I. et al. cited above). Accordingly, the fact that a large number of P450 enzymes have been identified, and that sequence alignment studies, along with computer models of crystal structures of the enzymes, have allowed the identification of regions of the P450s that may vary with no change in function alone does not give guidance sufficient guidance to one of skill in the art to identify additional BAS1 polypeptides that have a high likelihood of functioning in the same manner as BAS1 functions, as only a single cytochrome P450 polypeptide having the functional characteristics of BAS1, i.e. BAS1, is disclosed or known.

Applicants maintain that the breadth of the claims is not unduly broad in view of their disclosure of an exemplary gene sequence and the abundant functional and structural

characterization of the gene and its expression. In addition, Applicants point out that the claims as currently amended require that the sequence is a cytochrome P450 which carries with it known structural, functional and sequence limits, require that the cytochrome P450 use as its substrate active brassinosteroids, and clearly define a function that may be easily screened. (reply pages 12-13)

The Examiner maintains that the breadth of the claims is unduly broad in view of the fact that the rejected claims encompass the use of a multitude of unknown and undisclosed gene sequences obtained from any source that encode a cytochrome P450 which converts in any unspecified manner any unspecified active brassinosteroid to any unspecified inactive brassinosteroid. Applicants' disclosure of a single gene sequence from a single species of organism encoding a polypeptide belonging to an art recognized class of proteins does not contravene the breadth of the rejected claims because, as discussed above, cytochrome P450 proteins are known to be functionally diverse. The Examiner also maintains that while the disclosed screening process is within the technical abilities of one skilled in the art, it has not been established that the disclosed screening process may be readily employed to obtain other sequences encoding other polypeptides having the functional characteristics of BAS1, as only a single cytochrome P450 polypeptide having the functional characteristics of BAS1, i.e. BAS1, is disclosed or known.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35, 38 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 35, 38 and 41 are indefinite in the recitation of "the oligonucleotide of SEQ ID NO:1". There is insufficient antecedent basis for this limitation in the claims, or in claims 1, 12 and 22 from which they depend.

Claim Rejections - 35 USC § 102

Claims 12-13, 15, 17-18, 21-23, 25, 27-29 and 31 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mangold et al. (Plant Science, Vol. 96, pages 129-136, 1994), for the reasons of record set forth in the office action mailed June 3, 2004.

Applicants' arguments filed November 3, 2004 have been fully considered but they are not persuasive.

Applicants maintain that while Mangold et al. teach a cytochrome P450 enzyme in the CYP72 family that is in the same family as the basl gene disclosed in the present application, the cytochrome P450 disclosed in Mangold et al. does not use an active brassinosteroid as a substrate, as the substrate for the polypeptide encoded by the *Catharanthus roseus* gene, i.e., the gene disclosed in Mangold et al., is loganin, as taught by Irmler S. et al. (Indole alkaloid biosynthesis in *Catharanthus roseus*: new enzyme activities and identification of cytochrome P450 CYP72A1 as secologanin synthase. Plant J. 2000 Dec;24(6):797-804, included in the enclosed IDS), and loganin is not an active brassinosteroid. Applicants maintain that Mangold et al. thus fail to teach a polypeptide that is a cytochrome P450 which uses an active brassinosteroid

as a substrate, and that Mangold et al. therefore fail to anticipate the claimed invention. (reply page 13)

The rejection is maintained for the following reasons. First, the rejected claims do not require that a BAS1 polypeptide use an active brassinosteroid as a substrate; the rejected claims require that a BAS1 polypeptide "convert" an active brassinosteroid to an inactive brassinosteroid, which conversion does not find support in the specification as originally filed as set forth above under 35 USC 112.

Second, while Irmler et al. disclose loganin as a substrate for the *Catharanthus roseus* cytochrome P450 taught by Mangold et al., Irmler et al. do not disclose loganin as its sole substrate, or that the *Catharanthus roseus* cytochrome P450 taught by Mangold et al. cannot use an active brassinosteroid as a substrate. In this regard the Examiner notes that that some cytochrome P450 enzymes are known to have broad substrate specificity. See, for example, Mast N. et al. (Broad substrate specificity of human cytochrome P450 46A1 which initiates cholesterol degradation in the brain. Biochemistry. 2003 Dec 9;42(48):14284-92) and Shimada Y. et al. (Brassinosteroid-6-oxidases from *Arabidopsis* and tomato catalyze multiple C-6 oxidations in brassinosteroid biosynthesis. Plant Physiol. 2001 Jun;126(2):770-9).

Third, Applicant's specification indicates at page 11 lines 20-24 that the *Catharanthus roseus* cytochrome P450 taught by Mangold et al. is a BAS1 polypeptide within the meaning of the invention:

> "The term "BAS1 polypeptide" as used herein means the BAS1 polypeptide having the amino acid sequence of SEQ ID NO:2, as well as functional fragments thereof, along with other homologous plant cytochrome P450s, such as CYP72A from *Catharanthus roseus* (Madagascar periwinkle), which has about 42% sequence identity with BAS 1 at the amino acid level and the CYP72 chibi2 from Arabidopsis."

Claim Rejections - 35 USC § 103

Claims 20, 30 and 32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mangold et al. (Plant Science, Vol. 96, pages 129-136, 1994) in view of Persans et al. (Plant Physiology, 1995, Vol. 109, pages 1483-1490), and in further view of Lyznik et al. (The Plant Journal, 1995, Vol. 8, No. 2, pages 177-186), for the reasons of record set forth in the office action mailed June 3, 2004.

Applicants' arguments filed November 3, 2004 have been fully considered but they are not persuasive.

Applicants maintain as set forth above under 35 USC 102 that the cytochrome P450 disclosed in Mangold et al. does not use an active brassinosteroid as a substrate, as the substrate for the polypeptide encoded by the *Catharanthus roseus* gene, i.e., the gene disclosed in Mangold et al., is loganin, and loganin is not an active brassinosteroid. Applicants further maintain that Persans et al. and Lyznik et al. do not cure the deficiencies of Mangold et al., because neither Persans et al. nor Lyznik et al. teach or suggest a cytochrome P450 which uses an active brassinosteroid as a substrate, such that there is no prima facie case of obviousness for lack of one of the elements of the claims. (reply page 14)

The rejection is maintained as set forth above under 35 UDC 102. First, the rejected claims do not require that a BAS1 polypeptide use an active brassinosteroid as a substrate; the rejected claims require that a BAS1 polypeptide "convert" an active brassinosteroid to an inactive brassinosteroid, which conversion does not find support in the specification as originally filed as set forth above under 35 USC 112.

Second, while Irmler et al. disclose loganin as a substrate for the *Catharanthus roseus* cytochrome P450 taught by Mangold et al., Irmler et al. do not disclose loganin as its sole substrate, or that the *Catharanthus roseus* cytochrome P450 taught by Mangold et al. cannot use an active brassinosteroid as a substrate. In this regard the Examiner notes that that some cytochrome P450 enzymes are known to have broad substrate specificity. See, for example, Mast N. et al. (Broad substrate specificity of human cytochrome P450 46A1 which initiates cholesterol degradation in the brain. Biochemistry. 2003 Dec 9;42(48):14284-92) and Shimada Y. et al. (Brassinosteroid-6-oxidases from *Arabidopsis* and tomato catalyze multiple C-6 oxidations in brassinosteroid biosynthesis. Plant Physiol. 2001 Jun;126(2):770-9).

Third, Applicant's specification indicates at page 11 lines 20-24 that the *Catharanthus roseus* cytochrome P450 taught by Mangold et al. is a BAS1 polypeptide within the meaning of the invention:

> "The term "BAS1 polypeptide" as used herein means the BAS1 polypeptide having the amino acid sequence of SEQ ID NO:2, as well as functional fragments thereof, along with other homologous plant cytochrome P450s, such as CYP72A from *Catharanthus roseus* (Madagascar periwinkle), which has about 42% sequence identity with BAS 1 at the amino acid level and the CYP72 chibi2 from Arabidopsis."

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins
Examiner
Art Unit 1638

CC

Cynthia Collins 1/11/05